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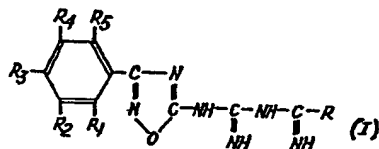


(54) IMPROVEMENTS IN OR RELATING TO OXADIAZOL-5-YL
 BIGUANIDE DERIVATIVES, METHOD FOR THEIR
 PREPARATION AND PHARMACEUTICAL COMPOSITIONS
 CONTAINING THEM

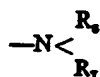
(71) I, JAN MARCEL DIDIER ARON-SAMUEL, a French Citizen of 116, Rue Carnot, 92 Suresnes, France, do hereby declare the invention for which I pray that a patent may be granted to me and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new biguanide derivatives having interesting pharmacological properties, to a method for their preparation and to a pharmaceutical composition containing the same as active ingredient.

The new derivatives of this invention have the formula:

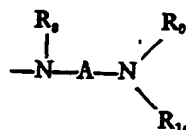


in which R_1 , R_2 , R_3 , R_4 , and R_5 , which may be the same or different, are selected from hydrogen, halo, alkyl, alkoxy, monohaloalkyl and polyhaloalkyl (particularly trifluoromethyl) or two adjacent groups may form an alkylene-dioxy (particularly methylene-dioxy) bridge; and R is (a) a group



in which R_6 and R_7 , which may be the same or different, each represent hydrogen, alkyl, allyl or a heterocyclic group (particularly piperidino or morpholino) which may be substituted with at least one alkyl group, or, together with the nitrogen atom to which they are attached, R_6 and R_7 form a 5- or 6-

membered heterocycle which may contain another heteroatom, and may be substituted with at least one group selected from alkyl, allyl, hydroxy, alkoxy, phenyl, alkylphenyl and halophenyl; or (b) a group:



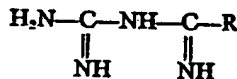
in which R_8 is hydrogen or alkyl, A is straight- or branched-chain alkylene and R_8 and R_9 , which may be the same or different, each represent straight- or branched-chain alkyl or, together with the nitrogen atom to which they are attached, form a 5-, 6- or 7-membered heterocycle which may be substituted with at least an alkyl group and which may contain another heteroatom.

The invention includes also within its scope the quaternary ammonium derivatives of compounds of the formula (I) and the acid addition salts thereof with inorganic and organic acids.

In the derivatives of the invention, the alkyl and alkoxy groups or moieties contain preferably from 1 to 6 carbon atoms.

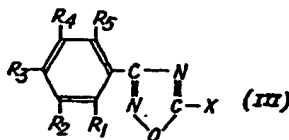
The alkylene groups contain preferably from 2 to 6 carbon atoms.

The invention relates also to a method for the preparation of derivatives of the formula (I), their salts and quaternary ammonium derivatives, comprising reacting a biguanide of the formula:



(II)

in which R is as above defined, with an oxadiazole derivative having the formula:



in which R₁, R₂, R₃, R₄, and R₅ have the above-defined meanings and X is halogen or a trihalomethyl radical.

Examples of halogens for X or the trihalomethyl group are particularly chlorine, bromine and iodine, chlorine being preferred.

This reaction may be conducted in basic media (such as sodium hydroxide, potassium hydroxide or sodium or potassium carbonate) in water or alcohols, or preferably in the presence of an aromatic solvent (e.g. benzene or toluene) or of a halogenated aliphatic solvent (e.g. methylene chloride or chloroform).

Biguanide (II) may be added in salt form (particularly as the hydrochloride). The reaction occurs at moderate temperature.

The resulting bases are generally solids which may be recrystallized from solvents such as alcohols, ethers and nitriles. The products readily give salts with inorganic and organic acids, which may be recrystallized from alcohols by conventional procedures well known to those skilled in the art.

When the derivatives of the formula (I) are capable of forming quaternary ammonium derivatives, these will be obtained by conventional procedures also well known to those skilled in the art.

The starting compounds of the formulae (II) and (III) are known products, or may be prepared by known methods, for example by the methods disclosed in the article by M. Noël, R. Prugnard and G. Patereau in C.R. Acad.Sci. Paris 268, 1407-1409, 1969.

The following non-limiting examples are given to illustrate the method for the preparation of the compounds of the invention.

Table I given after the examples provides a non-limiting list of derivatives of this invention prepared by the above-mentioned method, with their melting points by capillary tube. In the second column, for the purpose of simplicity, only the nature of the substituents of

the phenyl nucleus of the oxadiazole derivatives are given when present.

Example 1.

Into a reactor are added 100 ml of distilled water, 35 g of 3-dibutylaminopropyl-biguanide and 30 ml of methylene chloride. Pure caustic soda lye (d=1.33; 30 ml) is added thereto while maintaining the temperature at 15°C. A solution of 5-chloro-3-phenyl-1,2,4-oxadiazole (18 g) in methylene chloride (70 ml) is then added thereto, over 10 minutes. The temperature of the mixture increases to 35°C. The reaction mixture is stirred for one hour. The organic phase is decanted and washed with water (15 ml), and is then dried over sodium sulfate. The solvent is evaporated off, to give 49 g of orange oil which is dissolved in acetonitrile (100 ml). This solution, filtered whilst hot, gives on cooling a crystalline precipitate. Thus are obtained 18.9 g of 1-(3-dibutylaminopropyl)-5-(3-phenyl-5-oxadiazolyl)-biguanide (Derivative LA 2244). M.p.=112-114°C (capillary tube).

The hydrochloride melts at 163°-165°C.
The fumarate melts at 134°-135°C.

Example 2.

Into a reactor are added 31 g of 3-dibutylaminopropyl-biguanide and 60 ml of acetonitrile. The mixture is warmed to 30°C and 3-m-chlorophenyl-5-trichloromethyl-1,2,4-oxadiazole (29.7 g) dissolved in acetonitrile (40 ml) are added to the resulting solution. Stirring is maintained for 4 hours. The solvent is removed *in vacuo* and the resulting oil is solidified from absolute alcohol (100 ml). The resulting solid is recrystallized from acetonitrile (100 ml), to give 27 g of 1-(3-dibutylaminopropyl)-5-(3-m-chlorophenyl-5-oxadiazolyl)-biguanide (Derivative LA 2258). M.p.=101°-103°C.

Example 3.

Into a reactor are added 8.3 g of 1-(3-dibutylaminopropyl)-5-(3-phenyl-5-oxadiazolyl)-biguanide and 25 ml of acetone. The mixture is warmed until dissolution is complete, and 2.8 g of methyl iodide are then added thereto. After concentration and working up with acetone (15 ml), 6 g of 1-(1-dibutylmethyl-ammonio-3-propyl)-5-(3-phenyl-5-oxadiazolyl)-biguanide iodide are obtained. M.p. 105°C.

TABLE I

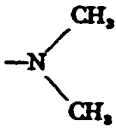
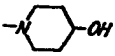
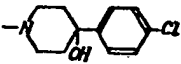

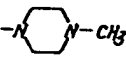
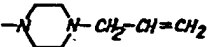
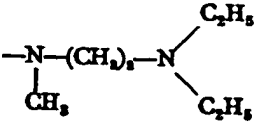
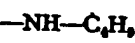
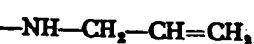
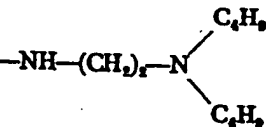
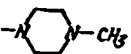
Compound No.	Substituent of the phenyl group	R	Form	M.P. °C capillary tube
LA 2241	none		base	226—227
LA 2263	none		base	173—174
LA 2261	none		base	251
LA 2255	none		base	223—224
LA 2240	none		base	216—219
LA 2246	none		base	176—177
LA 2248	none		base	136—137
LA 2242	none		base	167
LA 2253	none		base	168—169
LA 2256	none		base	94—96

TABLE I (continued)

Compound No.	Substituent of the phenyl group	R	Form	M.P. °C capillary tube
LA 2247	none		base	147—148
LA 2254	none		base	153—154
LA 2243	none		base	110—112
LA 2252	none		base	100—102
LA 2244	none		base hydrochloride fumarate	112—114 163—165 134—135
LA 2259	R ₁ =F		base	120
LA 2258	R ₁ =Cl		base	101—103
LA 2251	none		base	162—164
LA 2260	none		base	193—195

TABLE I (continued)

Compound No.	Substituent of the phenyl group	R	Form	M.P. °C capillary tube
LA 2257	none	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \\ \text{—NH—CH—(CH}_2\text{)}_3\text{—N—} \\ \quad \quad \quad \\ \text{CH}_3 \quad \quad \quad \text{C}_2\text{H}_5 \end{array}$	base	134—135
LA 2101	none	$\begin{array}{c} \text{C}_4\text{H}_9 \\ \\ \text{—NH—(CH}_2\text{)}_3\text{—N}^+\text{—C}_4\text{H}_9 \text{ Br}^- \\ \\ \text{CH}_3 \end{array}$	quaternary ammonium salt	143—145
LA 2100	none	$\begin{array}{c} \text{C}_4\text{H}_9 \\ \\ \text{—NH—(CH}_2\text{)}_3\text{—N}^+\text{—C}_4\text{H}_9 \text{ I}^- \\ \\ \text{CH}_3 \end{array}$	quaternary ammonium salt	105
LA 2264	R ₃ =CH ₃		base	203
LA 2265	R ₃ =Cl	$\begin{array}{c} \text{C}_4\text{H}_9 \\ \\ \text{—NH—(CH}_2\text{)}_3\text{—N—} \\ \quad \quad \quad \\ \quad \quad \quad \text{C}_4\text{H}_9 \end{array}$	base	137—138

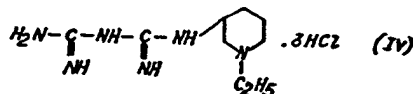
Among the derivatives listed in Table I, the following are particularly interesting:

- 1 - (3 - dibutylaminopropyl) - 5 - (3 - phenyl - 5 - oxadiazolyl) - biguanide (LA 2244); 1 - morpholino - 5 - (3 - phenyl - 5 - oxadiazolyl) - biguanide (LA 2255); 1 - (5 - diethylamino - 2 - pentyl) - 5 - (3 - phenyl - 5 - oxadiazolyl) biguanide (LA 2257); 1 - (3 - dibutylaminopropyl) - 5 - (3 - m. chlorophenyl - 5 - oxadiazolyl) - biguanide (LA 2258) and 1 - [(4 - hydroxy - 4 - parachlorophenyl) - piperidino] - 5 - (3 - phenyl - 5 - oxadiazolyl) - biguanide (LA 2261).

- 15 Among the biguanides of the formula (II) used for the preparation of the derivatives of the formula (I) set forth in Table I above, some are believed to be new chemical compounds.

- 20 Said new biguanides are the following:

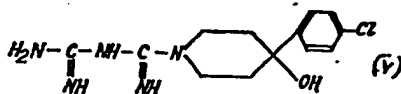
- 1) 3 - (N - ethyl - piperidinyl) - biguanide trihydrochloride, having the formula:



M.p (cap.)=253.5°C

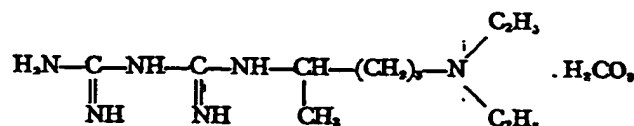
- 2) the biguanide having the formula:

25



M.p (cap.)=240—242°C

- 3) (5 - diethylamino - 2 - pentyl) - biguanide (carbonate) having the formula:



(VI)

M.p.=125°C (dec.)

Results of a pharmacological and toxicological investigation conducted with derivatives of the formula (I) are set forth below for illustrative purposes. The words "Metherzine" and "Cardiazole" are registered Trade Marks.

I — Pharmacological investigation.

1. Spasmolytic effect:

This effect was evidenced by the following techniques:

a) *On the isolated duodenum of rat:* As an example, 0.5 γ/ml of LA 2244 opposes the contraction of the duodenum of rat produced by 50 γ/ml of barium chloride, whereas 3 γ/ml of papaverin are required to produce this action. All other products of the series exhibit this property, to varying degrees.

Also, 0.5 γ/ml of LA 2244, LT 2259, LA 2265, LA 2100 or LA 2101 opposes the contraction of the duodenum of rat produced by 0.1 γ/ml of acetylcholine, whereas 7.5 γ/ml of papaverin are required to produce this action. All the other products of the series exhibit this property, to varying degrees.

b) *On the gall bladder of anesthetized guinea-pig:*

The method of J.R. Boissier and J.J. Chivot

(J.Physiol, Paris, 51, 408—409 (1959)) is used. The pylorus is tied and the apex of the gall bladder cathetized (1) as well as the duodenum just below the bile duct (2). An isotonic saline solution maintained at 37°C is perfused through (1) into the gall bladder and collected from (2).

The collection is made over periods of 2 minutes and weighed. A spasm of the sphincter of Oddi is induced by an intravenous injection of Carbachol (10 γ/Kg).

The flow is then interrupted in control animals 4 to 7 minutes after the injection for 4 to 9 minutes; it takes 10 to 16 minutes to return to its basic level.

When the products of the invention are injected into the duodenum (50 to 100 mg/Kg) 10 minutes before carbachol, then the flow is not interrupted, but lessened. Therefore those drugs relieve the spasm of the sphincter of Oddi. The results obtained are summarized in Table II below.

In fact, the effects on the biliary system are not limited to an antispasmodic action. There exists concomitantly a true increase of the volume of bile secreted, and therefore a stimulation of choleresis.

	Controls	LA 2244 50mg/kg intra- duodenal	LA 2257 100mg/kg intra- duodenal	LA 2258 100mg/kg intra- duodenal	LA 2259 100mg/kg intra- duodenal	LA 2261 100mg/kg intra- duodenal	LA 2261 100mg/kg oral route	LA 2100 100mg/kg intra- duodenal
Time to apparent inter- ruption of the perfusion	4-7 min.	0	0	0	0	0	0	0
Duration of this interruption	4-9 min.	Decrease of the rate of flow, but no interruption	ditto in only 2/4	ditto in all animals	slight decrease of the rate of flow	0	0	Decrease of the rate of flow, but no interruption
Delay before total resumption of the rate of flow	10-16 min.	5 min.	8 min.	14 min.	11 min.	Subsequent rate of flow is slightly higher	—	8 min.

c) On the spontaneous contractions of the uterus of the female rat, *in situ*, LA 2244 at a dosage of 2 mg/kg i.v. produces a 70% decrease of the amplitude of the spontaneous contractions during 30 minutes.

5

Method according to Langenhorn and Schmidt: On the contractions of the uterus of the female rat, *in situ*, induced by a 40 γ /kg i.v. *Methergine* injection, LA 2244 at a dosage of 2 mg/kg i.v. produces a 70% decrease of the amplitude of the contractions during a period of time of 90 minutes.

10

The other products of the formula (I) give comparable results under the same conditions.

15

d) On the isolated heart of rabbit or guinea-pig perfused through the aorta by the retrograde route, according to Langendorff's technique, there is noted, with said compounds, an increase of the coronary rate of flow which is powerful, extended, and highly superior to that of the reference materials.

20

Thus, at 1 γ /ml, LA 2244 opposes totally the coronary-constrictive action of 100 γ /ml of barium chloride, and reverses this action at 10 γ /ml.

25

The results obtained are set forth in Table III.

TABLE III

Action of BaCl ₂ 100 γ/ml on the coronary rate of flow	-40%
Action of a mixture of BaCl ₂ 100 γ/ml and LA 2244 at 1 γ/ml on the coronary rate of flow	0
Action of a mixture of BaCl ₂ 100 γ/ml and LA 2244 at 10 γ/ml on the coronary rate of flow	+50%
Action of a mixture of BaCl ₂ 100 γ/ml and papaverin at 1 γ/ml on the coronary rate of flow	-20%
Action of a mixture of BaCl ₂ at 100 γ/ml and papaverin at 10 γ/ml on the coronary rate of flow	+25%

Also, in coronary perfusion experiments, LA 2265 exhibits a vasodilator activity superior to that of papaverin.

5 2. Analgesic and anti-inflammatory effect

This effect was evidenced by means of the following tests:

10 a) On pain induced in mice by an intraperitoneal injection of 3% acetic acid, the derivatives of the formula (I) produce an analgesia which is at least equal and frequently superior to that of acetylsalicylic acid at an equivalent dosage. Thus, LA 2247, 15 LA 2248, LA 2251 and LA 2265 have an effect comparable with that of acetylsalicylic acid at dosages that are from 2 to 5 times lower.

20 b) On exudation produced in mice by the intra-pleural injection of an aqueous 0.5% Evans Blue solution (Weisbach Method, J. Med. Chem. 6, 91 (1963)), the subcutaneous injection of the derivatives of this invention is followed by a decrease in the volume of the exudate.

25 c) On the oedema induced by injection in the rat's paw of a 1% carrageenane suspension, ingestion of 100 mg/kg of LA 2244 is followed by a 52% decrease of the oedema.

The other derivatives of the formula (I) produce similar effects, at varying degrees.

30 At the same dosage, the decrease produced on the oedema by phenylbutazone is only 40%.

3. Anti-malarial action

On oral administration at a dosage of 200mg/kg, LA 2244, LA 2258 and LA 2259 35 prevent the death of mice infested with *Plasmodium berghei* (A. Quevauviller and J. W. Louw, Ann. Pharm. Fr., 13, 20 (1955)).

4. Protective action against strychnine

Derivatives LA 2241 and LA 2255 have a 40 substantial protective action against convulsions and death produced by the injection of strychnine. For example: the following results were obtained on lots of 10 reference mice administered 1.5 mg/kg of strychnine by the 45 intraperitoneal route:

intraperitoneal route:

	Convulsions	Dead
Reference animals	10	6
LA 2241 (100 mg/kg per os)	3	1
LA 2241 (200 mg/kg per os)	1	0
Reference animals	9	9
LA 2255 (100 mg/kg per os)	7	7
LA 2255 (200 mg/kg per os)	1	1

This is an effect produced at the level of muscular contractility, since Cardiazole (pentylene-tetrazole) - induced convulsions, chloral- and hexobarbital-induced sleep, activity, and equilibrium on a rotating rod are not influenced by said derivatives.

The decerebrate rigidity induced in rat by section of the nervous system between the bulb and the mesocephalon is suppressed for one hour by LA 2255 (200 mg/kg per os).

II — Toxicological investigation

The derivatives of the formula (I) have low toxicity and there exists a substantial margin of safety between the therapeutic doses and the toxic doses.

The LD₅₀, calculated according to the method of Kärber and Behrens, is given in mg/kg in the following Table IV.

TABLE IV

Product	Oral route	Subcutaneous route	Intraperitoneal route
LA 2243	1200	900	320
LA 2244	1500	>4000	240
LA 2246	>1000	> 500	300
LA 2247	500	300	—
LA 2248	200	500	150
LA 2251	800	700	—
LA 2252	500	500	160
LA 2253	350	800	—
LA 2254	500	180	—
LA 2255	>1000	>1000	—
LA 2256	>1000	> 100	—
LA 2257	900	500	—
LA 2258	1250	> 500	—
LA 2259	>1000	1080	75
LA 2260	>1500	1050	> 500
LA 2261	>2000	> 500	> 500
LA 2100	>2000	450	35
LA 2241	>1000	>1000	—
LA 2265	>1000	>1000	—

Chronic toxicity was studied in young rats with LA 2244 during a period of time of 3 months, at dosage of 10 mg/kg, 50 mg/kg and 200 mg/kg, by the oral route.

No effect was noted on growth, on the weight of the organs, on the blood count, the blood picture, or on azotemia.

Histological slides obtained from the heart, the lungs, the spleen, the liver, the suprarenal glands, the genital glands, the kidneys, the stomach, from a segment of the small and large intestines, from the thyroid, the bladder and the pancreas show the integrity of such organs. It is apparent from the above investigation

that the derivatives of the formula (I) possess therapeutically useful properties.

Thus, they are useful for the relief of spasms of the unstriated muscles and the syndromes they produce.

On administration to man in the form of capsules (400 mg) of suppositories (200 mg) LA 2244 was found to have an outstanding activity in painful syndromes of colitis, of biliary colic, of hiatal hernia, of premenstrual pains and in two atrociously painful cases of pancreatitis. Tolerance was perfect and the derivative was found to be free from the defects (such as dryness of the mouth and disorders of accommodation) of usual antispasmodic drugs of atropine type.

Said derivatives are also useful in the treatment of malaria. Finally, their anti-inflammatory activity permits their use in the various forms of rheumatism.

In addition, tests carried out with LA 2255 during neurological contractures gave satisfactory results.

Thus, the invention relates also to a pharmaceutical composition comprising, as active ingredient, a derivative of aforementioned formula (I), or a quaternary ammonium derivative or a pharmaceutically acceptable salt of the derivative of the formula (I), together with a pharmaceutically acceptable vehicle.

The composition may be formulated for oral, rectal or parenteral administration, the active ingredient being combined with the usual pharmaceutical carriers or excipients.

Thus, for oral administration, the composition may be formulated for example as tablets, coated tablets, granules, capsules, syrups and drinkable solutions. It may be interesting to coat the tablets with an enteric or non-enteric coating.

For rectal administration, the composition may be formulated as suppositories with the conventional vehicles, such as cocoa butter and its synthetic substitutes.

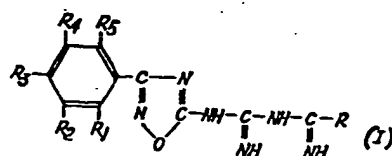
For parenteral administration, the composition may be formulated in ampoules or vials containing a solution or suspension of the active ingredient in sterile liquids, for example isotonic aqueous solutions, or oils.

In the unit dosage forms of the composition, such as tablets, suppositories or ampoules injectable by any other route than the intravenous route, the derivative, or its salt, or its quaternary ammonium derivative, comprising the active ingredient, will be used generally at unit doses of from about 25 mg to about 900 mg.

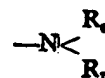
A daily dosage regimen will be, for example, from 150 mg to 5 g of active ingredient by the oral or rectal route, and from 1 mg to 100 mg, particularly from 25 mg to 100 mg, by the parenteral route.

WHAT I CLAIM IS:—

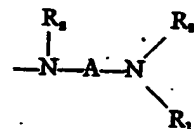
1. Biguanide derivatives having the formula:



in which R_1 , R_2 , R_3 , R_4 and R_5 , which may be the same or different, are selected from hydrogen, halo, alkyl, alkoxy, monohaloalkyl and polyhaloalkyl or two adjacent groups may form an alkylene-dioxy bridge and R is (a) a group



in which R_4 and R_7 , which may be the same or different, each represent hydrogen, alkyl, allyl or a heterocyclic group which may be substituted with at least one alkyl group, or, together with the nitrogen atom to which they are attached, R_4 and R_7 form a 5- or 6-membered heterocycle which may contain another heteroatom, and may be substituted with at least one group selected from alkyl, allyl, hydroxy, alkoxy, phenyl, alkylphenyl and halo-phenyl; or (b) a group



in which R_8 is hydrogen or alkyl, A is straight- or branched-chain alkylene and R_9 and R_{10} , which may be the same or different, each represent straight- or branched-chain alkyl or, together with the nitrogen atom to which they are attached, form a 5-, 6- or 7-membered heterocycle which may be substituted with at least one alkyl group and which may contain another heteroatom; their quaternary ammonium derivatives and acid addition salts with inorganic or organic acids.

2. Derivatives as claimed in claim 1, wherein the heterocycles are optionally substituted piperidino or morpholino groups.

3. Derivatives as claimed in claim 1 or 2, wherein any alkyl and alkoxy group or moiety present contains from 1 to 6 carbon atoms and, when present, the alkylene group A contains from 2 to 6 carbon atoms.

4. 1 - (3 - Dibutylaminopropyl) - 5 - (3-phenyl - 5 - oxadiazolyl) - biguanide and its pharmaceutically acceptable acid addition salts.

5. 1 - Morpholino - 5 - (3 - phenyl - 5-oxadiazolyl) - biguanide and its pharmaceutically acceptable acid addition salts.

6. 1 - (5 - Diethylamino - 2 - pentyl) - 5-

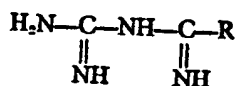
(3 - phenyl - 5 - oxadiazolyl) - biguanide and its pharmaceutically acceptable acid addition salts.

5 7. 1 - (3 - Dibutylaminopropyl) - 5 - (3 - m - chlorophenyl - 5 - oxadiazolyl) - biguanide and its pharmaceutically acceptable acid addition salts.

8. 1 - [(4 - Hydroxy - 4 - parachlorophenyl) - piperidino] - 5 - (3 - phenyl - 5 - oxadiazolyl) - biguanide and its pharmaceutically acceptable acid addition salts.

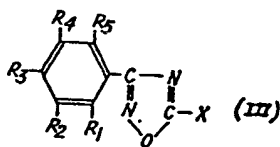
9. Derivatives as claimed in claim 1 as hereinbefore specifically disclosed, other than those claimed in any of claims 4—8.

15 10. A process for the preparation of derivatives as claimed in claim 1, comprising reacting a biguanide having the formula:



(II)

in which R is as defined in claim 1, with an
20 oxadiazole derivative having the formula:



in which R₁, R₂, R₃, R₄ and R₅ are as defined in claim 1 and X is halogen or trihalomethyl.

11. A process as claimed in claim 10, wherein X is chlorine or trichloromethyl. 25

12. A process as claimed in claim 10 or 11, wherein the biguanide of the formula (II) is used in salt form.

13. A process as claimed in claim 10, substantially as hereinbefore described with reference to any of the Examples. 30

14. Biguanide derivatives as claimed in claim 1 whenever made by the process of any of claims 10—13.

15. A pharmaceutical composition comprising, as active ingredient, a derivative of formula (I) as claimed in claim 1, or a quaternary ammonium derivative or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable vehicle. 35 40

16. A pharmaceutical composition as claimed in claim 15, in unit dosage form for oral, rectal or parenteral administration.

17. A pharmaceutical composition as claimed in claim 16, wherein each unit dose contains from 25 mg to 900 mg of active ingredient. 45

18. A pharmaceutical composition as claimed in any of claims 15—17 wherein said derivative of formula (I) is as claimed in any of claims 4—8. 50

19. A pharmaceutical composition as claimed in claim 15, substantially as hereinbefore described.

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